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Impact of sample collection participation on the validity of estimated measures of association in the National Birth Defects Prevention Study when assessing gene-environment interactions

Mary M. Jenkins¹, Jennita Reefhuis¹, Amy H. Herring², and Margaret A. Honein¹¹National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA²Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA

Abstract

To better understand the impact that nonresponse for specimen collection has on the validity of estimates of association, we examined associations between self-reported maternal periconceptional smoking, folic acid use, or pregestational diabetes mellitus and six birth defects among families who did and did not submit buccal cell samples for DNA following a telephone interview as part of the National Birth Defects Prevention Study (NBDPS). Analyses included control families with live born infants who had no birth defects ($N = 9,465$), families of infants with anorectal atresia or stenosis ($N = 873$), limb reduction defects ($N = 1,037$), gastroschisis ($N = 1,090$), neural tube defects ($N = 1,764$), orofacial clefts ($N = 3,836$), or septal heart defects ($N = 4,157$). Estimated dates of delivery were between 1997 and 2009. For each exposure and birth defect, odds ratios and 95% confidence intervals were calculated using logistic regression stratified by race-ethnicity and sample collection status. Tests for interaction were applied to identify potential differences between estimated measures of association based on sample collection status. Significant differences in estimated measures of association were observed in only four of 48 analyses with sufficient sample sizes. Despite lower than desired participation rates in buccal cell sample collection, this validation provides some reassurance that the estimates obtained for sample collectors and noncollectors are comparable. These findings support the validity of observed associations in gene-environment interaction studies for the selected exposures and birth defects among NBDPS participants who submitted DNA samples.

Keywords

birth defects; gene-environment interaction; selection bias; validation studies

Correspondence: Mary M. Jenkins, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 4770 Buford Highway, Mailstop E-86, Atlanta, GA30341, USA. MQJ2@cdc.gov.

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Orcid: Mary M. Jenkins, <http://orcid.org/0000-0002-4399-1348>

1 Introduction

Appropriate generalization of results from gene-environment interaction studies requires that estimated measures of association obtained from the subgroup who collected specimens are similar to those from the larger study population. Self-selection bias can occur when participation rates are low and differ among subgroups for which different associations exist between the exposure and outcome, leading to inaccurate interpretation of results (Morimoto, White, & Newcomb, 2003).

Among families eligible for the National Birth Defects Prevention Study (NBDPS), 37% of case and 31% of control families provided both interview data and buccal (cheek) cell samples for at least one family member. In addition to decreased power that results from suboptimal participation rates, there is concern about self-selection bias given the documented differences in submitting buccal cell samples based on demographic, lifestyle, or other factors (Crider, Reefhuis, Woomert, & Honein, 2006; Glidewell et al., 2014).

The main public health impact of NBDPS genetic analyses is to identify gene-environment interactions that might provide the opportunity for prevention. We assessed associations between maternal periconceptional smoking, periconceptional use of vitamins containing folic acid, and pregestational diabetes mellitus, type 1 or 2 (diabetes), and six selected birth defects using tests of interaction to determine whether participation in sample collection among NBDPS participants impacted the observed associations.

2 Methods

2.1 Study population

The NBDPS is a population-based case-control study of genetic and nongenetic risk factors for major structural birth defects conducted in 10 states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) (Reefhuis et al., 2015). Eligible infants had at least one of approximately 30 structural birth defects (case infants) or no major birth defects (control infants). Case infants were ascertained from existing population-based surveillance systems and could be live born, stillborn, or terminations. Clinical geneticists reviewed medical records using standard case definitions to determine eligibility (Rasmussen et al., 2003). Infants with chromosomal abnormalities or single gene disorders were excluded. Live born control infants were selected randomly from birth certificates or birth hospital data from the same geographic region and time period. A computer-assisted telephone interview was conducted with mothers between 6 weeks and 24 months after their estimated date of delivery (EDD) to collect information on pregnancy exposures, including information on periconceptional (between 1 month before and the first 3 months of pregnancy) maternal smoking, folic acid use, and diabetes. Interviews were conducted in English or Spanish after obtaining verbal consent. Following completion of the interview, mothers were sent cytobrushes (two per participant) to collect buccal cell samples from themselves, their infant (if living), and their infant's biological father. Institutional Review Boards at the Centers for Disease Control and Prevention and each study site approved the NBDPS.

Families of infants with one or more of six birth defects (neural tube defects (NTDs), orofacial clefts, gastroschisis, limb reduction defects, anorectal atresia/stenosis, or septal heart defects) and control families with EDDs between 1997 and 2009, who had completed all or part of the maternal interview, and either did (sample collector) or did not (sample noncollector) provide buccal cell samples from the mother, infant, or both were included. Infants with more than one of the selected birth defects were included in multiple case groups. Eligible case infants could have other birth defects in addition to the six under study. One mother who provided samples for herself reported using an egg donor, and her data were removed from analyses of sample collectors. Selected exposures and birth defects were chosen based on their use in NBDPS gene-environment interaction studies, sample sizes, and previous reported associations (Cleves, Hobbs, Zhao, Krakowiak, & MacLeod, 2011; Correa et al., 2008; Hackshaw, Rodeck, & Boniface, 2011; Hobbs et al., 2014; Jenkins et al., 2014; Lupo et al., 2012; Tang, Cleves et al., 2015; Tang, Hobbs et al., 2015). We considered the associations between three exposures and six phenotypes to assess whether sample collection participation impacts the observed associations over a range of sample sizes.

2.2 Statistical analyses

Genetic analyses are typically stratified by race-ethnicity due to differences in minor allele frequencies and genetic effects. Maternal race-ethnicity was used as a proxy for infant race-ethnicity. Frequency distributions for each exposure and phenotype were calculated for sample collectors and noncollectors stratified by maternal race-ethnicity (non-Hispanic white (NHW), non-Hispanic black (NHB), and Hispanic), and differences were assessed using chi-square tests. We used logistic regression to calculate crude and adjusted (for continuous maternal age at delivery) odds ratios (ORs) and 95% confidence intervals (CIs) for each exposure and birth defect stratified by sample collection status and race-ethnicity. Maternal age at delivery (<25 years or ≥25 years) was also assessed as a potential effect modifier for gastroschisis analyses (Jones et al., 2016). Analyses of NTDs and each assessed exposure included additional potential confounders; maternal body mass index (<18.5; 18.5–24.99; 25–29.99; ≥30), maternal education (<12 years or ≥12 years), study site, periconceptional alcohol consumption (any or none), and each exposure that was not the main exposure of interest.

Tests of interaction were applied to identify differences between estimated measures of association of sample non-collectors and collectors for each exposure and birth defect according to the method of Altman and Bland (2003). A ratio of the ORs (OR of noncollectors/OR of collectors) and corresponding 95% CIs were calculated. *P*-values for interaction (*P*_{int}) were calculated from *Z* scores using a significance level of <0.05 and a two-tailed hypothesis. This method tests the null hypothesis of no significant difference between the two ORs by comparing the *Z* score to the standard normal distribution. To test for interaction, subgroups (and their effect estimates) must be independent. Thus, we compared estimates of sample noncollectors and collectors rather than comparing sample collectors to all those who completed an interview. Analyses were not conducted when stratum sizes fell below two participants. No adjustments to *P*-values for multiple comparisons were made to the primary analyses but were considered in sensitivity analyses

using the *p.adjust* function in the stats package of R (Benjamini & Hochberg, 1995). IBM SPSS Statistics Version 21.0 was used to analyze data in the primary analyses.

3 Results

3.1 Sample collection rates

Among control mothers who completed the interview, 4,522 women (48%) submitted samples for themselves ($n = 157$; 3%), their infant ($n = 43$; 1%), or both ($n = 4,322$; 96%) (Table 1). Among case mothers, sample collection rates differed by birth defect. Collection rates also differed by race-ethnicity. With few exceptions, case-control status significantly affected sample collection rates overall and when stratified by race-ethnicity.

3.2 Frequency distributions of selected exposures

Periconceptional smoking was reported less often and folic acid use more often in sample collectors compared to noncollectors with a few exceptions (Table 2). This difference was significant among NHW mothers of control infants and of four infant case groups for smoking, and among NHW mothers of infants with gastroschisis or anorectal atresia/stenosis for folic acid use.

Diabetes was reported significantly more often in sample collectors compared to noncollectors among NHW mothers of infants with anorectal atresia/stenosis or septal heart defects and significantly less often in collectors compared to noncollectors among NHB mothers of infants with orofacial clefts (Table 2).

3.3 Measures of association and tests of interaction

No significant differences were observed between estimated measures of association from sample noncollectors and collectors for smoking and each birth defect when data were stratified by race-ethnicity (Table 3). Significant differences were observed between estimated measures of association from sample noncollectors and sample collectors for folic acid use among NHW mothers and their infants with gastroschisis or anorectal atresia/stenosis (Table 4). Significant differences were also observed for diabetes among NHB mothers and their infants with orofacial clefts and among NHW mothers and their infants with septal heart defects (Table 5). Small numbers precluded some analyses of diabetes. Results for ORs (crude or age-adjusted) were similar for all analyses; adjusted ORs were reported.

Tests of interaction among families of infants with gastroschisis and smoking or folic acid use stratified by maternal age at delivery were completed for all three racial-ethnic groups (data not shown). Small numbers precluded completion of similar tests for diabetes. Significant differences between ORs from sample noncollectors and collectors were observed in analyses of folic acid use among older NHW mothers ($P_{\text{int}} = 0.03$) and were borderline among younger mothers ($P_{\text{int}} = 0.07$). Among older mothers, ORs were significantly reduced in sample noncollectors who reported folic acid use (OR = 0.36, 95% CI: 0.17, 0.77; $P = 0.009$) and consistent with the null in sample collectors (OR = 1.65, 95%

CI: 0.52, 5.30; $P = 0.40$). No significant differences were observed among families with NHB or Hispanic mothers.

Similar results were observed among families of infants with NTDs and each exposure after adjusting for additional confounders and adjusting for maternal age at delivery only (data not shown).

4 Discussion

Our data reduce concerns about the potential impact of selection bias due to sample collection in gene-environment interaction studies for selected birth defects (NTDs, orofacial clefts, gastroschisis, limb reduction defects, anorectal atresia/stenosis, and septal heart defects) and exposures (maternal periconceptional smoking, folic acid use, and diabetes) among NBDPS participants. No significant differences in estimated measures of association between sample noncollectors and collectors were observed in 44 of 48 analyses with sufficient sample sizes. Due to suboptimal response rates, it is difficult to claim that there is no selection bias; however, these findings might assuage concerns over different underlying estimates based on sample collection.

To our knowledge, no studies have assessed the potential effect of noncollection on the validity of estimated measures of association for gene-environment interaction studies. The goal of this paper was not to assess individual associations but differences between estimates of associations of sample collector and noncollector subgroups. The main effects of the exposures on birth defect risk do not have to be strong to assess these differences, and the exposures chosen for this study had varied effects. We used a statistical test of interaction (Altman & Bland, 2003) to compare these estimates with a null hypothesis of equal estimates.

With only one exception, no exposure distributions differed significantly by sample collection among families with NHB or Hispanic mothers. Among families with NHW mothers, nine of 21 distributions differed significantly by sample collection. However, only four of the 10 exposure and birth defect combinations that differed significantly by sample collection had significant interaction terms.

We observed four significant interaction terms out of 48 tests. If all 48 tests were independent and there was truly no interaction, the probability of at least one false positive is over 90%. Thus, it was unclear if the significant results were true differences or type I errors. To mitigate these concerns, we conducted false discovery rate analysis (Benjamini & Hochberg, 1995) and found no significant interaction terms (data not shown). Although multiple testing corrections cannot distinguish between individual false and true positive findings, they do reduce the inherent inflation of the false-positive rate due to repeated testing. However, because a lack of significant interactions was reassuring, investigators using NBDPS specimens and interview data might be well-served to assess selection bias for each exposure and outcome combination included in their analyses.

Because maternal age is a strong risk factor for gastroschisis, analyses of maternal smoking or folic acid use were stratified by and adjusted for maternal age at delivery with similar results, suggesting that maternal age was not acting as an effect modifier.

Specimen nonresponse limits the ability to identify genetic variants with small to moderate effects that might interact with environmental factors to modify disease risk, more so than in other epidemiological research. These analyses assessed the impact of selection bias on estimates of association for environmental risk factors and did not directly assess the impact on gene-environment interactions. To expand our findings to gene-environment interactions assumes that there is limited genetic heterogeneity between sample collectors and noncollectors. Although we know from previous studies (Crider et al., 2006; Glidewell et al., 2014; McQuillan, Porter, Agelli, & Kington, 2003; Moorman et al., 2004) that race and ethnicity are factors that consistently affect whether a participant collects and submits specimens, genetic studies typically stratify data by race and ethnicity to account for genetic heterogeneity during analyses. Other factors observed to affect collection of specimens for genetic research, such as age, income, and education, should have limited genetic heterogeneity between sample collectors and noncollectors. Challenges to assessing gene-environment interaction using NBDPS data include relatively small numbers of infants with each birth defect, suboptimal sample collection rates, and self-reported exposure data collected up to 2 years after an infant's EDD. We considered combining case groups to increase statistical power. However, because the causes of birth defects are so varied, analyses with combined case groups would be of limited value to other etiological studies of birth defects. Although there were many exposures (e.g., other maternal health conditions, medications, other vitamins, diet, stress, alcohol, illicit drugs, maternal, and paternal occupation) and over 30 birth defects included in the NBDPS, we limited these analyses to associations between three exposures and six birth defects that were included in NBDPS gene-environment interaction studies to help inform future studies. The NBDPS is the largest birth defects risk factor study to collect biological specimens in the United States. It has a population-based, multi-state ascertainment that included participants who were representative of their base populations (Cogswell et al., 2009), specimen collection quantity and quality that improved over time (Gallagher et al., 2011), and clinicians who reviewed each case using standard definitions (Rasmussen et al., 2003). After establishing that nonresponse in buccal cell collection and submission was not a random event (Glidewell et al., 2014), there were some concerns over how representative risk estimates limited to sample collectors would be. This study allays concerns by showing that the majority of estimates for sample collectors and noncollectors are comparable, providing some reassurance as gene-environment interactions are assessed using NBDPS samples and interview data.

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Table 1
Case and control families by race-ethnicity and sample collection participation status, National Birth Defects Prevention Study, 1997–2009

	NHW			NHB			Hispanic			Total		
	Sample noncollector ^a	Sample collector ^b	<i>P</i>	Sample noncollector	Sample collector	<i>P</i>	Sample noncollector	Sample collector	<i>P</i>	Sample noncollector	Sample collector	<i>P</i>
Controls	2,818 (48)	3,105 (52)		761 (67)	367 (33)		1,364 (57)	1,050 (43)		4,943 (52)	4,522 (48)	
Neural tube defects	293 (30)	673 (70)	<0.005	109 (61)	69 (39)	0.10	285 (46)	335 (54)	<0.005	687 (39)	1,077 (61)	<0.005
Orofacial clefts	1,095 (43)	1,445 (57)	<0.005	175 (65)	94 (35)	0.47	474 (46)	553 (54)	<0.005	1,744 (45)	2,092 (55)	<0.005
Gastroschisis	257 (42)	351 (58)	0.01	63 (61)	41 (39)	0.16	171 (45)	207 (55)	<0.005	491 (45)	599 (55)	<0.005
Limb reduction defects	245 (40)	366 (60)	<0.005	68 (57)	52 (43)	0.02	154 (50)	152 (50)	0.04	467 (45)	570 (55)	<0.005
Anorectal atresia/stenosis	219 (45)	266 (55)	0.32	69 (66)	35 (34)	0.83	140 (49)	144 (51)	0.02	428 (49)	445 (51)	0.08
Septal heart defects	1,155 (47)	1,297 (53)	0.70	385 (68)	181 (32)	0.83	614 (54)	525 (46)	0.15	2,154 (52)	2,003 (48)	0.67

NHW indicates non-Hispanic white; NHB, non-Hispanic black.

^aSample noncollectors completed all or part of the maternal interview and samples were not submitted for the mother or infant; percentage in parentheses.

^bSample collectors completed the maternal interview and samples were submitted for the mother, infant or both; percentage in parentheses.

Table 2
Case and control families by race-ethnicity, participation in sample collection, and selected exposures, National Birth Defects Prevention Study, 1997–2009

	Non-Hispanic white				Non-Hispanic black				Hispanic						
	Sample noncollector ^a		Sample collector ^b		Sample noncollector		Sample collector		Sample noncollector		Sample collector				
	N	%	N	%	P	N	%	N	%	P	N	%	N	%	P
Maternal periconceptional ^c smoking															
Controls	724	26.4	619	20.0	<0.005	109	15.1	54	14.7	0.87	107	8.4	84	8.0	0.75
Neural tube defects	77	26.8	117	17.4	<0.005	19	18.4	12	17.4	0.86	27	10.0	27	8.1	0.42
Orofacial clefts	334	31.3	383	26.5	0.01	30	17.6	20	21.3	0.47	49	10.9	53	9.6	0.50
Gastroschisis	141	58.3	172	49.0	0.03	13	22.0	13	31.7	0.28	23	14.4	30	14.5	0.98
Limb reduction defects	69	28.9	81	22.3	0.07	16	25.8	8	15.4	0.17	19	12.9	13	8.6	0.22
Anorectal atresia/stenosis	61	28.9	61	22.9	0.14	14	21.2	5	14.3	0.40	18	13.2	12	8.3	0.19
Septal heart defects	330	29.5	323	24.9	0.01	87	23.6	35	19.3	0.25	65	11.1	59	11.3	0.95
Maternal periconceptional use of vitamins containing folic acid															
Controls	2,546	93.0	2,852	92.9	0.86	576	79.1	298	81.9	0.28	988	76.0	819	79.0	0.09
Neural tube defects	261	92.6	603	92.1	0.80	79	77.5	52	76.5	0.88	218	79.0	249	75.7	0.34
Orofacial clefts	963	90.2	1,316	92.2	0.08	134	79.3	75	79.8	0.92	350	75.9	402	73.4	0.35
Gastroschisis	211	86.1	325	93.4	<0.005	43	74.1	33	80.5	0.46	121	74.7	157	77.0	0.61
Limb reduction defects	217	90.8	336	92.1	0.59	51	82.3	41	80.4	0.80	117	78.5	121	82.3	0.41
Anorectal atresia/stenosis	176	84.2	239	90.5	0.04	52	83.9	31	91.2	0.32	107	76.4	113	80.1	0.45
Septal heart defects	1,003	89.5	1,170	91.4	0.11	289	79.4	148	81.8	0.51	443	75.3	406	77.5	0.40
Pregestational diabetes mellitus, type 1 or 2															
Controls	20	0.8	12	0.4	0.09	5	0.7	4	1.2	0.45	7	0.6	10	1.1	0.19
Neural tube defects	3	1.1	12	1.9	0.37	2	2.0	1	1.5	0.80	4	1.7	6	2.0	0.77
Orofacial clefts	14	1.4	18	1.3	0.92	15	9.4	2	2.2	0.03	15	3.7	16	3.3	0.73
Gastroschisis	1	0.4	1	0.3	0.81	1	1.6	1	2.5	0.75	0	0.0	0	0.0	NC
Limb reduction defects	10	4.5	11	3.1	0.39	1	1.6	4	8.2	0.10	2	1.5	5	3.6	0.28
Anorectal atresia/stenosis	0	0.0	11	4.4	<0.005	4	6.3	2	6.3	0.99	7	5.8	9	7.5	0.59

	Non-Hispanic white						Non-Hispanic black						Hispanic					
	Sample noncollector ^a			Sample collector ^b			Sample noncollector			Sample collector			Sample noncollector			Sample collector		
	N	%		N	%	P	N	%		N	%	P	N	%		N	%	P
	25	2.3		46	3.8	0.04	15	4.3		13	7.9	0.10	27	5.1		25	5.7	0.69
Septal heart defects																		

^aSample noncollectors completed all or part of the maternal interview and samples were not submitted for the mother or infant.

^bSample collectors completed the maternal interview and samples were submitted for the mother, infant, or both.

^cPericonceptual indicates any exposure during the month before or the first 3 months of pregnancy.

NC indicates not calculated because of zero values.

Table 3
Tests of interaction for adjusted^a odds ratios of the associations between periconceptional^b maternal smoking and selected birth defects by race-ethnicity and sample collection participation status,^c National Birth Defects Prevention Study, 1997–2009

Defect category	Race-ethnicity	Sample collector	Adjusted OR	95% CI	Ratio of ORs	95% CI	Z	P_{int}
Neural tube defects	NHW	No	0.98	0.74, 1.30	1.22	0.85, 1.76	1.10	0.27
		Yes	0.80	0.64, 1.01				
	NHB	No	1.30	0.76, 2.23	1.04	0.43, 2.51	0.09	0.93
		Yes	1.25	0.62, 2.49				
	Hispanic	No	1.27	0.81, 1.99	1.25	0.66, 2.36	0.67	0.50
		Yes	1.02	0.65, 1.61				
Orofacial clefts	NHW	No	1.24	1.05, 1.45	0.86	0.69, 1.07	-1.39	0.17
		Yes	1.45	1.25, 1.69				
	NHB	No	1.24	0.79, 1.93	0.78	0.38, 1.62	-0.67	0.50
		Yes	1.59	0.89, 2.81				
	Hispanic	No	1.35	0.94, 1.93	1.08	0.65, 1.80	0.30	0.77
		Yes	1.25	0.87, 1.79				
Gastroschisis	NHW	No	2.24	1.68, 2.98	1.09	0.74, 1.59	0.43	0.66
		Yes	2.06	1.61, 2.63				
	NHB	No	1.41	0.73, 2.72	0.64	0.24, 1.72	-0.88	0.38
		Yes	2.20	1.05, 4.61				
	Hispanic	No	1.61	0.97, 2.67	0.92	0.46, 1.84	-0.24	0.81
		Yes	1.75	1.09, 2.81				
Limb defects	NHW	No	1.17	0.87, 1.59	1.07	0.72, 1.62	0.34	0.73
		Yes	1.09	0.83, 1.42				
	NHB	No	1.92	1.05, 3.52	1.79	0.66, 4.91	1.13	0.25
		Yes	1.07	0.48, 2.40				
	Hispanic	No	1.63	0.97, 2.75	1.54	0.69, 3.43	1.05	0.29
		Yes	1.06	0.58, 1.96				
Anorectal atresia or stenosis	NHW	No	1.14	0.83, 1.57	0.97	0.62, 1.52	-0.11	0.91

Defect category	Race-ethnicity	Sample collector	Adjusted OR	95% CI	Ratio of ORs	95% CI	Z	P_{int}
		Yes	1.17	0.86, 1.60				
	NHB	No	1.56	0.83, 2.91	1.59	0.49, 5.17	0.77	0.44
		Yes	0.98	0.36, 2.65				
	Hispanic	No	1.71	1.00, 2.92	1.58	0.69, 3.63	1.48	0.14
		Yes	1.08	0.57, 2.04				
Septal heart defects	NHW	No	1.22	1.04, 1.43	0.94	0.75, 1.18	-0.55	0.58
		Yes	1.30	1.11, 1.53				
	NHB	No	1.77	1.29, 2.42	1.24	0.70, 2.18	0.74	0.46
		Yes	1.43	0.89, 2.29				
	Hispanic	No	1.40	1.01, 1.94	0.92	0.57, 1.49	-0.34	0.74
		Yes	1.52	1.07, 2.16				

^a Adjusted for maternal age at delivery (continuous).

^b Periconceptual indicates 1 month before or during the first 3 months of pregnancy.

^c Sample collectors completed the maternal interview and samples were submitted for the mother, infant, or both; sample noncollectors completed all or part of the maternal interview and samples were not submitted for the mother or infant.

OR indicates odds ratio; CI, confidence interval; P_{int} , P -value of interaction; NHW, non-Hispanic white; NHB, non-Hispanic black.

Tests of interaction for adjusted^a odds ratios of the associations between periconceptional^b use of vitamins containing folic acid and selected birth defects by race-ethnicity and sample collection participation status,^c National Birth Defects Prevention Study, 1997–2009

Table 4

Defect category	Race-ethnicity	Sample collector	Adjusted OR	95% CI	Ratio of ORs	95% CI	Z	P _{int}
Neural tube defects	NHW	No	0.98	0.61, 1.57	1.08	0.61, 1.91	0.25	0.80
		Yes	0.91	0.66, 1.25				
	NHB	No	0.83	0.50, 1.39	1.19	0.53, 2.67	0.41	0.68
		Yes	0.70	0.37, 1.31				
	Hispanic	No	1.13	0.82, 1.56	1.38	0.89, 2.13	1.44	0.15
		Yes	0.82	0.61, 1.10				
Orofacial clefts	NHW	No	0.71	0.55, 0.92	0.77	0.54, 1.10	-1.45	0.15
		Yes	0.92	0.72, 1.16				
	NHB	No	0.97	0.64, 1.48	1.14	0.56, 2.33	0.36	0.72
		Yes	0.85	0.48, 1.52				
	Hispanic	No	0.98	0.76, 1.26	1.38	0.97, 1.96	1.80	0.07
		Yes	0.71	0.56, 0.91				
Gastroschisis	NHW	No	0.86	0.56, 1.31	0.44	0.23, 0.83	-2.52	0.01
		Yes	1.95	1.21, 3.13				
	NHB	No	1.01	0.54, 1.89	0.89	0.31, 2.54	-0.21	0.83
		Yes	1.13	0.49, 2.60				
	Hispanic	No	1.24	0.83, 1.84	1.03	0.60, 1.79	0.12	0.91
		Yes	1.20	0.82, 1.75				
Limb defects	NHW	No	0.72	0.45, 1.15	0.77	0.42, 1.44	-0.81	0.42
		Yes	0.93	0.62, 1.39				
	NHB	No	1.28	0.64, 2.54	1.47	0.53, 4.08	0.74	0.46
		Yes	0.87	0.41, 1.85				
	Hispanic	No	1.16	0.77, 1.76	0.92	0.50, 1.70	-0.26	0.79
		Yes	1.26	0.80, 1.99				
Anorectal atresia or stenosis	NHW	No	0.40	0.26, 0.59	0.53	0.29, 0.97	-2.05	0.04

Defect category	Race-ethnicity	Sample collector	Adjusted OR	95% CI	Ratio of ORs	95% CI	Z	P_{int}
	NHB	Yes	0.75	0.48, 1.16				
		No	1.31	0.65, 2.67	0.58	0.14, 2.37	-0.76	0.45
	Hispanic	Yes	2.26	0.67, 7.63				
		No	0.99	0.66, 1.50	0.96	0.52, 1.77	-0.13	0.90
Septal heart defects	NHW	Yes	1.03	0.66, 1.61				
		No	0.62	0.49, 0.79	0.74	0.53, 1.03	-1.77	0.08
	NHB	Yes	0.84	0.66, 1.06				
		No	0.98	0.72, 1.34	1.05	0.60, 1.85	0.18	0.86
	Hispanic	Yes	0.93	0.58, 1.48				
		No	0.94	0.75, 1.18	1.07	0.76, 1.50	0.38	0.70
		Yes	0.88	0.68, 1.13				

^a Adjusted for maternal age at delivery (continuous).

^b Periconceptual indicates 1 month before or during the first 3 months of pregnancy.

^c Sample collectors completed the maternal interview and samples were submitted for the mother, infant, or both; sample noncollectors completed all or part of the maternal interview and samples were not submitted for the mother or infant.

OR indicates odds ratio; CI, confidence interval; P_{int} , P -value of interaction; NHW, non-Hispanic white; NHB, non-Hispanic black.

Tests of interaction for adjusted^a odds ratios of the associations between pregestational diabetes mellitus, type 1 or 2 and selected birth defects by race-ethnicity and sample collection status,^b National Birth Defects Prevention Study, 1997–2009

Table 5

Defect category	Race-ethnicity	Sample collector	Adjusted OR	95% CI	Ratio of ORs	95% CI	Z	P _{int}
Neural tube defects	NHW	No	1.46	0.43, 4.94	0.31	0.07, 1.33	-1.58	0.11
		Yes	4.74	2.12, 10.61				
	NHB	No	2.77	0.53, 14.53				
		Yes	NC					
	Hispanic	No	2.73	0.79, 9.45	1.43	0.29, 7.16	0.44	0.66
		Yes	1.91	0.68, 5.32				
Orofacial clefts	NHW	No	1.88	0.94, 3.74	0.57	0.21, 1.57	-1.09	0.27
		Yes	3.29	1.58, 6.86				
	NHB	No	14.16	5.05, 39.71	7.57	1.01, 56.67	1.97	0.05
		Yes	1.87	0.33, 10.47				
	Hispanic	No	6.86	2.77, 17.00	2.29	0.68, 7.70	1.34	0.18
	Yes	3.00	1.34, 6.72					
Gastroschisis	NHW	No	NC					
		Yes	NC					
	NHB	No	NC					
		Yes	NC					
	Hispanic	No	NC					
		Yes	NC					
Limb defects	NHW	No	6.13	2.83, 13.29	0.75	0.24, 2.33	-0.49	0.62
		Yes	8.16	3.56, 18.68				
	NHB	No	NC					
		Yes	7.33	1.75, 30.76				
	Hispanic	No	2.78	0.57, 13.62	0.76	0.11, 5.27	-0.27	0.78
		Yes	3.64	1.21, 10.92				
Anorectal atresia or stenosis	NHW	No	NC					

Defect category	Race-ethnicity	Sample collector	Adjusted OR	95% CI	Ratio of ORs	95% CI	Z	P_{int}
		Yes	11.46	4.99, 26.30				
	NHB	No	9.17	2.38, 35.31	1.61	0.18, 14.78	0.42	0.67
		Yes	5.69	0.98, 33.02				
	Hispanic	No	10.69	3.64, 31.40	1.49	0.36, 6.20	0.54	0.59
		Yes	7.19	2.82, 18.38				
Septal heart defects	NHW	No	3.06	1.69, 5.54	0.32	0.13, 0.76	-2.59	0.01
		Yes	9.67	5.10, 18.32				
	NHB	No	6.29	2.27, 17.48	0.98	0.21, 4.55	-0.02	0.98
		Yes	6.41	2.04, 20.15				
	Hispanic	No	9.22	3.97, 21.44	1.76	0.57, 5.42	0.98	0.33
		Yes	5.25	2.49, 11.08				

^a Adjusted for maternal age at delivery (continuous).

^b Sample collectors completed the maternal interview and samples were submitted for the mother, infant, or both; sample noncollectors completed all or part of the maternal interview and samples were not submitted for the mother or infant.

OR indicates odds ratio; CI, confidence interval; P_{int} , P -value of interaction; NHW, non-Hispanic white; NHB, non-Hispanic black; NC, not calculated.